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(54) Title: **PROTEIN S PROTECTS THE NERVOUS SYSTEM FROM INJURY**

(57) **Abstract:** Protein S is a significant neuroprotectant when administered after focal ischemic stroke and prevents hypoxic/re-oxygenation injury. Purified human plasma-derived or recombinant protein S improves motor neurological function after stroke, and reduced brain infarction and edema. Protein S also enhances post-ischemic reperfusion and reduced brain fibrin and neutrophil deposition. Cortical neurons are protected from hypoxia/re-oxygenation-induced apoptosis. Thus, protein S and variants thereof are prototypes of a class of agents for preventing injury of the nervous system. In particular, a disease or other pathological condition (e.g., stroke) may be treated with such agents having one or more protein S activities (e.g., anti-thrombotic and anti-inflammatory activities, direct cellular neuronal protective effects) although the latter activities are not be required.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/30638

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : a61k 38/00

US CL : 514/12

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Dialog Search Terms: protein s, author search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	U.S. 5,405,946 (Griffin et al.) April 11 1995. Whole patent	1-5
X	U.S. 5,663,142 (Bouma et al.). September 2 1997. Whole patent.	1-5
X	U.S. Patent 5,804,181 (Eibil et al.) September 8, 1998. Whole patent. See especially claims 1 - 6.	1-5
X	U.S. 5,891,843 (Turecek et al.) April 6, 1999. Whole patent. See especially claim 8.	1-5
X,P	Cheng et al. 2002. Neuroprotective and anti-thrombotic effects of protein S in a murine model of stroke. Society for Neuroscience Abstract No. 390.13. Whole document.	1-5

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Name and mailing address of the ISA/US

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-5

Remark on Protest☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1 - 5, drawn to pharmaceutical compositions.

Group 2, claim(s) 6 - 18, drawn to methods of protecting cell types of a subject's nervous system.

Group 3, claim(s) 19 - 21, drawn to the use of protein S for the manufacture of a pharmaceutical composition.

Group 4, claim(s) 22, drawn to a method of screening for an agent which inhibits apoptosis.

Group 5, claim(s) 23, drawn to a method of producing an agent which inhibits apoptosis.

Group 6, claim(s) 24, drawn to an agent selected by a screening or production method.

The inventions listed as Groups 1 - 6 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I is drawn to a pharmaceutical composition comprising protein S or a variant thereof. Griffin et al. (US Patent 5,405,946, issued 11 April 1995) teach a variant of protein S (see claims) and contemplate the pharmaceutical compositions comprising the variant (see column 12, line 65 - column 13, line 54). The pharmaceutical composition of claim 1 is not a contribution over the prior art. Therefore, there is no special technical feature which links all inventions.